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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,290	VOLLMERS ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *73,80,81,89-91,95-97,106-112,115,116 and 122-124* is/are pending in the application.

4a) Of the above claim(s) *89-91 and 95-97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *73,80,81,106-112,115,116 and 122-124* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/23/10* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 73, 80, 81, 89-91, 95-97, 106-112, 115, 116 and 122-124 are all the pending claims for this application.

2 Claims 75, 100-105 and 117-120 were cancelled, Claims 73, 108 and 111 were amended and new Claims 122-124 were added in the Response of 7/12/10.

3. Claims 89-91 and 95-97 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim.

4. Claims 73, 80, 81, 106-112, 115, 116 and 122-124 are all the pending claims under examination.

5. Applicants amendments to the specification and claims have necessitated new grounds for objection and rejection. This Office Action is final.

Information Disclosure Statement

6. The IDS of 7/23/10 has been considered and entered. The examiner's initialed and signed copy of the 1449 forms is attached.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, second paragraph

7. The rejection of Claim 75 because it recites examples of cancer cells that are not recited in generic claim 73 is moot in view of the cancelled claim.

8. The rejection of Claim 75 because all of the recited species in Claim 75 are drawn to carcinomas that are broader in scope than any of the single, isolated cell lines of generic Claim 73 is moot for the cancelled claim.

Objections Maintained

Specification

9. The objection to the figure legend to Figures 10A and 10B for failing to describe the x- and y-axis labels for each of the panels is maintained.

The objection was set forth in the Office Action of 5/5/09 as follows:

"Applicants allege on p. 12 of the Response of 2/17/09 "In terms of the objection to Figures 10A and 10B for allegedly not describing the x- axis or y-axis, in view of the description of Figure 10A and 10B set forth on page 27, lines 16-25, the x-axis of 10A and 10B refer to tumor weight and tumor volume, respectively. As to the y-axis, in view of the description of Figure 10A and 10B it appears that this axis represents a particular mouse."

Response to Arguments

Closer inspection of both Figure 10A and 10B reveals that both the SAM-6 sample and control are both designated by the same "open" circle which does not permit the viewer to discern the effects of SAM-6 from the control in either panel. Further, it is still unclear how each of the test and control samples relates to the "particular mouse" on the y-axis and the corresponding "tumor weight and tumor volume, respectively" on the x-axis. Finally, it is not clear to the examiner how the y-axis can be particular mouse, especially for panel A where the scale appears in increasing 0.05 increments. This is the same for panel B where the scale increases by hundredth increments.

If Applicants can correct this error or omission without filing a new figure they are welcome to amend the specification. In this case, they are advised to carefully check the specification for original support in order to avoid a new matter issue.

Applicants are also requested to carefully check the other figures in the specification for similar inconsistencies (see for example, Figure 8) and which might be addressed by amending the specification.

The objection was maintained in the Office Action of 1/12/10 as follows:

"Applicants allegations on p.8 of the Response of 11/5/09 have been considered and are not found persuasive. Applicants allege "In particular, the description states that "According to Figure 10a the average weight of tumors of SAM-6 treated mice is 96.2 gram, while average weight of tumors of mice treated with the control antibody is 150.5 gram. Figure 10b shows that analysis of the volume of tumors corresponds to with the analysis of tumor weight. The average volume of tumors of SAM-6 treated mice is 126.3 mm3, while average volume of tumors of mice treated with control antibody is 158.2 mm3.""

Response to Arguments

The description provided by Applicants is inconsistent with the Y-axis which shows increasing increments of 0.5 (panel A) and 100 (panel B) of no disclosed unit and which does not correspond to the average tumor weight in grams depicted in the literal description. Also, the scatter plot is indecipherable for both the SAM antibody and the control as to what the average tumor volume/ tumor weight is with respect to the unlabeled x-axis.

Applicants' attorney has obfuscated the issue with arguments that do not address the outstanding objection, correct the outstanding material omission or advance prosecution. Any such arguments can only be construed by a

reasonable individual as a frustration of purpose to the advancement and compact prosecution of this application. The objection is maintained."

Applicants allegations on pp. 8 & 10-11 of the Response of 7/12/10 have been considered and are not found persuasive. Applicants allege "the error is obvious in view of the fact that one of skill in the art knows that the average weight of a mouse is about 20 grams, and therefore that it is impossible for a tumor to weigh 5-8 times more (i.e., about 100-160 grams) than the weight of the mouse itself". Thus the specification has been amended to recite that the tumor is measured in milli-grams and not by gram weight.

Response to Arguments

Applicants have provided no support in the originally filed application that the tumor weight instead corresponds to milli-grams rather than grams for the instant amended figure legend of Figure 10A and 10B. Their statement is unsubstantiated by reference art or declaration evidence that a tumor cannot exceed the normal weight of the animal. If the data in Figures 10A and 10B correspond to the in vivo experiment on p. 61, lines 5-17 of the specification, then Applicants have provided no reason to doubt or question that the tumor mass produced by the human pancreatic carcinoma cell line, BXPC-3, could greatly exceed the normal weight of the mouse.

Applicants amendment raises a new matter issue and the rejection is maintained.

Note: Applicants submission of the revised Figures 10A and 10B under Exhibit A in the Response of 7/12/10 does not meet the requirements for replacement drawings under

37 CFR 1.84. The revised Figures 10A and 10B have not been considered or entered as revised drawings. Accordingly, Exhibit A does not rectify or obviate the objection.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

10. The rejection of Claims 106 (and new Claim 123) under 35 U.S.C. 112, first paragraph, is maintained because the specification does not reasonably provide enablement for any anti-GRP78^{SAM-6} antibody having at least 95% identity to either the VL of SEQ ID NO:1 and/or the VH of SEQ ID NO:3 much less that the antibody variants would have specific and exclusive binding for any one antigen. Applicants have yet to disclose the antigen against which the SAM6 antibody binds and therefore any screening assays for an antibody having a specific and exclusive binding for the antigen are precluded.

For purposes of review, the rejection was set forth in the Office Action of 9/19/08 as follows:

> "Nature of the Invention/ Skill in the Art
> The claims are interpreted as broadly encompassing of an antibody or antigen binding fragment thereof with binding specificity for the antigen expressed on an adenocarcinoma of the lung, squamous cell lung carcinoma, intestinal type gastric carcinoma, diffuse type gastric carcinoma, adenocarcinoma of the colon, adenocarcinoma of the prostate, squamous cell carcinoma of the esophagus, adenocar cinoma of the esophagus, lobular carcinoma of the breast, ductal carcinoma of the breast, adenocarcinoma of the pancreas, adenocarcinoma of the ovary, and adenocarcinoma of the uterus, or that it binds to the following cell lines: BXPC-3,

23132/87, COLO-206F, COL0-699 or LOU-NH91, and where the antibody has: at least 75%, 80%, 85%, 90% or 95% identity to either the VL of SEQ ID NO:1 and/or the VH of SEQ ID NO:3, or a single VL domain (SEQ ID NO:1) or a single VH domain (SEQ ID NO:3), or a single CDR domain or less than the full complement of VL CDR1-3 and VH CDR1-3 from SEQ ID NO:1 and/or SEQ ID NO:3.

The relative skill in the art required to practice the invention is a molecular immunologist.

Disclosure in the Specification

The specification generally contemplates making antibodies on p. 29, line 16 to p. 34, line 21; generating antibody variants by DNA modifications on p. 34, line 23 to p. 36, line 26. The specification provides definitions for functional antibody fragments (p. 14, lines 14-25).

The specification discloses a single isolated antibody, SAM-6, selected from a library of antibodies generated by fusing lymphocytes from a human stomach adenocarcinoma patient (Table 1) with the heteromyeloma cell line HAB-1 to produce a trioma. At the time of filing, Applicants specification did not reveal the identity of the antigen but generally characterized the antigen immunohistochemical screening of SAM-6 against normal tissues and autologous tumor where the antigen was defined by the cancer cell-binding properties for the antibody (Example 2). SAM-6 showed no reactivity with normal tissues but different tumor tissues (Tables 3 and 4). Partial characterization of the antigen in Example 3 showed by Western blot analysis the antibody recognized proteins of 140 kDa (Figure 3A). Rauschert et al (Lab. Invest. 88:375-386 (2008)) later described the antigen as GRP78 and the epitope is an O-linked carbohydrate moiety. The sequence for SAM-6 was determined for VL and VH (Example 2). Sam-6 antibody was shown to induce apoptosis in the cell lines BXPC-3 and 23132/87 (Example 4); and inhibit proliferation of the cell line 23132/87 (Example 5).

The specification contemplates but does not specifically disclose working embodiments for just any of the antibody structures encompassed by the claims much less that any modified antibody would have the required properties of recognizing an adenocarcinoma of the lung, squamous cell lung carcinoma, intestinal type gastric carcinoma, diffuse type gastric carcinoma, adenocarcinoma of the colon, adenocarcinoma of the prostate, squamous cell carcinoma of the esophagus, adenocarcinoma of the esophagus, Iobular carcinoma of the breast, ductal carcinoma of the breast, adenocarcinoma of the pancreas, adenocarcinoma of the ovary, and adenocarcinoma of the uterus, or that it binds to the following deposited cell lines: BXPC-3, 23132/87, COLO-206F, COL0-699 or LOU-NH91.

Without sufficient guidance in the written description alone, the ordinary artisan could not practice making and using the myriad antibody embodiments encompassed by the claims because the specification and claims do not define which regions and domains are subject to variation, which regions or domains could tolerate the introduction of the variation, or the nature and extent of the variation. For example, the claims are not limited to whether the extent of variation comprises amino acid substitutions, insertions, deletions and combinations thereof so that the ordinary artisan could predict which variation would not compromise antigen binding specificity. The claims are not limited as to whether the variation occurs in the antigen binding domains or Fc regions, or the CDRs and/or framework domains. Thus it is not readily apparent from the specification or the original claims as filed, how the ordinary artisan could practice the invention without incurring undue experimentation in order to identify a reasonable number of working embodiments based on the extent of antibody variation encompassed by the claims. Further, the claims encompass antibody embodiments having structures that are generally viewed in the field of art as being non-operative or at least unpredictable as to their antigen affininty, namely, antibodies having single variable domains or those having fewer than the full complement of both VL and VH CDRs. Thus the ordinary artisan could not reduce to practice the myriad embodiments and expect to obtain a reasonable number of working embodiments absent undue experimentation at the levels of gene manipulation, antibody screening and bioassay performance.

Prior Art Status: Single CDR-domain Antibodies

The claims encompass isolated antibodies comprising a single CDR domain (and less than the full complement of VH/VL CDRs) from SAM-6 antibody. Applicants have not shown that any isolated any antibody comprising less than a full complement of VH/VL CDRs from a parent SAM-6 antibody would retain the antigen binding to any on the cell lines test in the assays. In fact there are numerous publications acknowledging that the conformation of CDRs as well as framework residues influence binding.

MacCallum *et al.* (J. Mol. Biol. 262:732-745 (1996)) analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.).

de Pascalis *et al.* (Journal of Immunology 169, 3076-3084 (2002)) demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right col.).

Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left col.).

The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset *et al.* (BBRC 307, 198-205, (2003)) which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset *et al.* also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and a framework residue located just before the H3 (see page 202, left col.).

Vajdos *et al.* (J. Mol. Biol. 320, 415-428 (2002)) additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left col.).

Holm *et al* (Mol. Immunol. 44: 1075-1084 (2007)) describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were involved in antigen binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract).

Chen *et al.* (J. Mol. Bio. 293, 865-881 (1999)) describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866).

Wu *et al.* (J. Mol. Biol. 294, 151-162 (1999)) state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation.

Thus, while one can make the statement that a single CDR makes a significant contribution in the antigen binding, the residues in these CDRs are not the only residues that influence binding and in fact the prior art as well as applicants own disclosure do not support that it was clearly established, that the a single CDR domain alone is sufficient to define the binding specificity of an antibody, and that multiple antibodies can predictably be generated having the same binding specificity based on a single CDR (or less than full complement of VH CDRs and VL CDRs).

Analyzing applicants own disclosure, which while it does contemplates divergent CDR residues, the only working example is the SAM-6 antibody having heavy chain CDRs paired with complementary light chain CDRs. Additionally, the data indicate that it is the frameworks and CDRs that contribute to antigen binding. Further, there are no examples of mixing or matching of the light chain CDRs or heavy chain CDRs and most importantly there is no working example of placing a single CDR domain of a heavy chain and/or a light chain in just any framework and producing an antibody that binds antigen as broadly claimed or suggested.

Prior Art Status: Conservative Amino Acid Substitutions within CDR/FR Residues

The claims encompass antibodies comprising VH domains, VL domains and CRDs which vary in the extent to which they resemble the corresponding domain in the parent SAM-6 antibody. This variation can comprise any number and kind of amino acid substitutions. It is not well established in the art that all variable domains are amenable to modifications much less that that substitutions are for conservative amino acids. Numerous publications acknowledge that conservative substitutions would in fact change the binding ability of antibodies if not substantially reduce the affinity.

Brummell *et al.* (Biochemistry 32:1180-1187 (1993)) found that mutagenesis of the four HCDR3 contact residues for the carbohydrate antibody (Salmomella B O-polysaccharide) in no instance improved affinity but 60% of the mutants resulted in a 10-fold drop in binding constant (affinity electrophoresis value of 0.85), while still other mutants were lower (Table 1 and p. 1183, Col. 2, ¶2 to p. 1184, Col. 1, ¶1). Brummell demonstrates that no substitution retained antigen binding affinity similar to the wild type antibody despite targeted, conservative substitutions in known contact sites.

Kobayashi *et al.* (Protein Engineering 12:879-844 (1999)) discloses that a scFv for binding a DNA oligomer containing a (6-4) photoproduct with Phe or Tyr substitutions at Trp 33 retained "a large fraction of the wild-type binding affinity, while the Ala substitution diminished antigen binding" (Table 1). However, Kobayashi notes "replacing Trp 33 with Phe or Ala alters the local environment of the (6-4) photodimer since binding is accompanied by large fluorescence increases that are not seen with the wild-type scFv" (p. 883, Col. 2, ¶3).

Burks *et al.* (PNAS 94:412-417 (1997)) discloses scanning saturation mutagenesis of the anti-digoxin scFv (26-10) which also binds digitoxin and digoxigenin with high affinity and with 42-fold lower affinity to ouabain. 114 mutant scFvs were characterized for their affinities for digoxin, digitonin, digoxignenin and oubain. Histogram analysis of the mutants (Figure 2) reveals that "not all residues are optimized in even high affinity antibodies such as 26-10, and that the absence of close contact with the hapten confers higher plasticity, i.e., the ability to tolerate a wider range of substitutions without compromising binding (p. 415, Col. 2, ¶4- p. 416, ¶1).

Brummell *et al.*, Kobayashi *et al.* and Burks *et al.* introduced conservative amino acid substitutions into CDRs to examine binding effects and demonstrate that any conservative substitution within any CDR cannot be made without affecting binding.

Jang *et al.* (Molec. Immunol. 35:1207-1217 (1998)) teach that single amino acid mutations to the CDRH3 of a scFV derived from 2C10, an anti-dsDNA autoantibody, reduced the binding activity about 20-50% compared to the unmutated scFv (Table 4).

Brorson *et al.* (J. Immunol. 163:6694-6701 (1999)) teach that single amino acid substitutions to the CDRs of IgM Abs for the bacterial protein, levan, are ablated.

Coleman (Research in Immunol. 145:33-36 (1994)) teaches that single amino acid changes within the interface of an antibody-antigen complex are important and that inasmuch as the interaction can tolerate amino acid sequence substitutions, "a very conservative substitution may abolish binding" while "in another, a non-conservative substitution may have very little effect on the binding" (p. 35, Col. 1, ¶1).

Prior Art Status for Single Variable Domain Antibodies

Smith-Gill et al. (J. Immunol. 139:4135-4144 (1987)) observed from chain recombination experiments that through interactions between the VH/VL pair, specificity for antigen is H chain determined, specific binding is increased when L chains of the same parental isotype are used, and that both H and L chains determine fine specificity.

Kumar et al. (J. Biol. Chem. 275:35129-35136 (2000)) discloses Fab molecules with anti-DNA (light chain) and anti-cardiolipin (heavy chain) binding activities, and that pairing of the partner chains is dependent on the particular H/L chain pairing.

Song et al. (Biochem Biophys Res Comm 268:390-394 (2000)) discloses that affinity and specificity of scFv for preS1 protein of HBV is dependent on S-S bond formation in conferring correct refolding of the fragments for retaining binding properties, and that L chains are predominant in antigen binding.

Therefore, selecting and producing just any variable domain substituted antibody with the ability to properly associate and assemble into a fully functional antibody which maintains the binding specificity for the original antigen would be highly unpredictable based on the methods described in the specification and the prior art disclosures.

Unpredictability/Undue Experimentation

The specification provides no direction or guidance regarding how to produce the genus of antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Furthermore, while the level of skill required to generate the antibodies is that of a molecular immunologist, the ordinary artisan would have been required to identify candidate amino acid residues for substitution in the FR and/or CDR domains, perform the mutagenesis on the FR and CDR domains, produce and express the modified antibodies, measure binding characteristics (e.g., binding specificity, equilibrium dissociation constant (K_D), dissociation and association rates (K_{off} and K_{on} respectively), and binding affinity and/or avidity compared with the parent antibody) in a BIAcore assay, and then finally perform bioassays to identify any one or more of the characteristics of the antibody. The technology to perform these experiments was available at the time of application filing, but the amount of experimentation required to generate even a single FR- and/or CDR-modified antibody meeting all of the claim limitations would not have been routine much less could one of ordinary skill in the art predict that any one or combination of all the FR and CDR amino acid substitutions encompassed by the claims would result in *just any* substituted antibody clone having retained the antigen binding activity (MPEP 2164.06, "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (In re Wands, 858 F.2d 731, 737, 8 USQP2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

The rejection was maintained in the Office Action of 9/19/08 as follows:

"Applicants' allegations on pp. 12-17 of the Response of 2/17/09 have been considered and are not found persuasive.

A) Applicants allege "there is no need for the skilled artisan to "predict which variation would not compromise antigen binding specificity" in advance in order to make variants and functional fragments because making variant antibodies and functional fragments and screening to determine those with binding activity was routine and well established at the time of the invention."

Boder et al. (Proc. Nat'l Acad. Sci._USA 97:10701 (2000) Exhibit A) describes directed evolution of scFv fragments using the method developed by Stemmer W. P., Nature 370:389 (1994). A large number of Fv sequences had improved binding affinity, with a dissociation rate greater than 1000 fold slower than the native non- mutagenized antibody (see, abstract).

Response to Arguments

The specification and the prior art reference does not identify 1) a complete structure, ii) partial structure, iii) physical and/or chemical properties, or iv) functional characteristics coupled with correlation between *structure and function* for the genus of antibodies that a) bind the same epitope as the SAM-6 antibody, b) inhibits cell proliferation of 23132/87 (DSMZ Accession No. ACC 201) cells and c) induces apoptosis of at least one of BXPC-3 (ATCC Accession No. CRL- 1687) and 23132/87 (DSMZ Accession No. ACC 201) cells (see MPEP 2105 and Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406).

B) Applicants allege "An antibody, by definition, includes three CDRs in at least a heavy chain variable region sequence. Consequently, as the claims are directed to antibodies that bind to an epitope of an antigen, which include 3 CDRs on the heavy chain variable region sequence, the ground for rejection relating to a single CDR is not relevant."

Response to Arguments

Applicants attention is drawn to pending Claims 86 and 111, each of which recite "wherein the antibody of antibody fragment includes *at least one* complementary-determining region (CDR)...". The phrase "at least one" is interpreted as there being only a single CDR domain from the VH and VL domain. Further, Claims 82-85, 102, 103, 109 and 110 are interpreted as being drawn to single variable domain antibodies, which as asserted in the previous Office Action are art-recognized as being unpredictable in binding properties.

It is noted that the features upon which applicant relies (i.e., An antibody includes three CDRs in at least a heavy chain variable region sequence) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

C) Applicants allege "In terms of the publications cited at pages 12-14 of the Action as evidence that conservative amino acid substitutions in the CDR/FR residues "change binding ability of antibodies if not substantially reduce the affinity," Applicants respectfully point out that the claims do not recite a particular binding affinity. Consequently, even if a change were to increase or decrease affinity for the epitope of the antigen expressed by at least one of the recited cells types, that antibody is included, provided binding is detectable by an assay."

To corroborate that substitutions within CDRs are tolerated, submitted Kipriyanov et al. (Protein Engineering 10:445 (1997)) report that a substitution of a cysteine residue by a serine within CDR3 of an antibody heavy chain variable region did not have an adverse effect on affinity.

To corroborate that substitutions within FRs are tolerated, Holmes et al. (J. Immunol. 167:296 (2001)) report several heavy chain variable region FR substitutions of an anti-lysozyme antibody did not destroy binding activity.

To corroborate that insertions and deletions of amino acid residues in heavy and light chain variable regions, including CDRs, are tolerated submitted Wilson et al. (J. Exp. Med. 187:59 (1998)) report a number of insertions and deletions of variable heavy chains that occur naturally during affinity maturation which are tolerated.

To further corroborate that insertions and deletions of amino acid residues in heavy and light chain variable regions, including CDRs, are tolerated Lantto and Ohlin (J. Biol. Chem. 277:45108 (2002)) report that single amino acid insertions or deletions of CDRs 1 and 2 of heavy chain variable region of an antibody were well tolerated.

Response to Arguments

The examiner appreciates the individual examples of modified antibody species that are taught in each of the references, where the modifications were specifically described and targeted for certain domains and residues. However, none of the instant claimed modifications are in any way described insofar as whether they occur in the CDR and/or framework domains, the kind of modifications, the residues effected by the modification, or those residues that are required as being essential for binding, etc. The claims encompass antibodies comprising a percent variation between the antibody VH/VL and/or CDR and/ or framework with respect to the VL and VH of SEQ ID NOS: 1 and 3, without providing a structure function correlation between the antibody sequence comprising the modifications and the function of the antibody. The claims encompass not only antibodies that are required to bind the epitope of the SAM-6 antibody but to have a functional, biological effect.

Applicants have not established by a preponderance of the evidence the structure/function correlation for the claimed antibodies that would enable the ordinary artisan to predict making and using the broad scope of antibodies with a reasonable degree of certainty absent further experimentation (See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus

by virtue of having disclosed a single species when … the evidence indicates ordinary artisans *could not predict the operability in the invention* of any species other than the one disclosed.").

The rejection was maintained in the Office Action of 1/12/10 as follows:

"Applicants allegations on pp. 9-13 of the Response of 11/5/09 have been considered and are not found persuasive.

A) Applicants allege methods of producing antibodies and amino acid variants without undue experimentation are disclosed in the specification (page 31, line 20, to page 36, line 26); and routine methods for detecting antibody binding to antigen or cell lines, as well as methods for measuring cell proliferation and apoptosis are disclosed in the specification (page 47, line 8 to page 49, line 10; page 55, line 26, to page 57, line 29; and page 66, line 10, to page 68, line 24)."

Response to Arguments

The specification may teach all of the methods available to generate and screen antibodies but the specification does not teach which of those methods would allow the ordinary artisan to predict the kind and extent of modification for the variable domains in order for the resultant claimed antibody to meet all of the functional requirements of the claims. For claims encompassing modified variable domains as in the instant case, Dufner (Trends Biotechnol. 24(11):523-29 (2006)) teaches: "specific structural information - on the antibody to be optimized, its antigen and their interaction- is rarely available or lacks the high resolution required to determine accurately important details such as side-chain conformations, hydrogen-bonding patterns and the position of water molecules" (p. 527, Col. 2, ¶1). Applicants specification and the evidence of record does not define specific structural information detailing the number of and exact position of hotspots in the CDRs which "can vary considerably from case to case and therefore cannot be predicted" (legend to Figure 2 of Dufner). Thus even with the availability of screening approaches as taught in the specification, Applicant's cited art and Dufner, the ordinary artisan could not predict the hotspots much less those residues critical for conferring specific antigen binding for any of the claimed CDRs and variable domains absent further additional information and experimentation. What does a sequence alignment for the variable domains, CDR regions or frameworks regions look like for a "reasonable" number of the modified antibodies that would guide the ordinary artisan in determining the important common shared or similar binding residues that confer specific antigen binding similar to the SAM-6 antibody? Are any hotspots present in the CDRs (or frameworks), what is the frequency of those hot spots and what are the positions of those hot spots? Applicants are requested to answer these questions in order to establish that the claims are enabled for the breadth and scope of the percent variation as claimed.

B) Applicants allege the claims are analogous to *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988), where the court held that screening hybridornas to determine those that produced monoclonal antibodies having a particular binding characteristic did not require undue experimentation. Likewise, undue experimentation would not be required to make variant antibodies and fragments that bind the epitope to which SAM-6 antibody binds given that 1) producing antibody variants and fragments was routine; and 2) cell binding, antibody competition, proliferation and apoptosis assays are disclosed in the specification and were also routine assays,in the art at the time of the invention.

Response to Arguments

Applicants rely on the *Wands* decision to support their position that the amount of experimentation required to produce the instant claimed antibody would be routine and not unduly burdensome.

The Examiner submits that the production techniques involved in making the inventive antibody comprising any variation of the antibody variable domains and retaining the binding characteristics for the antigen of interest and common to the SAM-6 antibody, are not even remotely related to the production techniques involved in making and screening the monoclonal antibodies of Wands invention. Wands antibody production and screening of the monoclonal antibodies occurred prior to 1981. Wands technology involved generating a panel of highly specific IgM Mabs against a single known antigen, HbsAg. In 1981, Wands did not even contemplate systems for calculating a) variable domain modifications, and b) amino acid frequency alignment, much less the technology to produce a recombinant antibodies as instantly claimed. Wands only assay for screening the monoclonal antibodies was a commercially available radioimmunoassay kit, and further screening to select IgM isotype and binding affinity constant for the monoclonal antibodies. This is in distinct contrast to the instant claimed antibodies whose cognate antigen is not even defined in the claims or the specification. The only identity for the antigen of the instant claims is that the SAM-6 antibody should also recognize the same epitope on the same antigen.

Further, Applicants have ignored the Wands Court discussion of what constitutes a "reasonable" number of working embodiments. *Wands* does not provide any guidance as to what a reasonable number of working examples should be. Specifically the Court stated:

"No evidence is presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen."

With the state of the art at the time of the Wands' invention in mind, the Court states "This process entails immunizing animals, fusing lymphocytes from immunized animals with myeloma cells to make hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics." Applicants reliance on the *Wands* decision in the instant case does not appear to appreciate any of the technical advancements that occurred between the early 1980's and the techniques required to produce the instant claimed invention at the time of application filing. Finally, because *Wands* does not provide any guidance as to what a reasonable number of working embodiments should be for an unpredictable and technically complex art, Applicants have not overcome the rejection.

Applicants attorney continues to obfuscate the issue with arguments that do not address the outstanding rejection, provide the identity of the genus of antigens encompassed by the claims or advance prosecution towards a showing that a reasonable number of the infinite genus of antibodies recognizing the infinite number of antigens expressed on the claimed cell lines could possibly be enabled at the time of filing.

C) Applicants allege claims where no antibody has ever been produced are routinely granted by the Patent Office. Thus, if claims covering antibodies where no antibody has been made and therefore where no antibody structure is known have been granted, surely knowledge of antibody structure or predicting the effects of particular variations on antibody binding is not required to satisfy the enablement requirement under 35 U.S.C. § 112.

Response to Arguments

The examiner submits that the arguments are nebulous and frustrate the advancement of the prosecution. Applicants have not cited a single example of any such antibody patent issued by the Office and to which they have privileged access to the prosecution proceeding in order to advance the assertion that claims to any modified antibody is enabled.

D) Applicants allege methods of producing variant antibodies and identifying those having binding activity were at the time of the invention, previously submitted Exhibit A (Boder et at. (Proc. Nat'l Acad. Sci. USA 97:10701 (2000)) describe directed evolution of scFv fragments, and generation of a large number of Fv sequences with improved binding affinity compared to non-mutagenized antibody.

Response to Arguments

Again, because the specification and the claims do not even identify the antigen(s) to which the SAM-6 antibody much less the purified antibody binds and which antigen(s) is commonly expressed by the cell lines of Claim 73, that comparison to Boder is irrelevant. In Broder, a single known parent antibody against a known antigen was mutagenized and assayed for binding. Here the skilled artisan would be required to test numerous and indefinite numbers of antigens expressed by the claimed cell lines in order to find an antigen to which both the purified and SAM-6 antibody could bind. The unduly burdensome amount of experimentation to screen all possible antigens would not fall within what *Wands* considers routine experimentation.

E) Applicants allege "The facts and Dr. Vollmers' conclusions based upon the facts are summarized in the Declaration, Paragraphs 20-24."

Response to Arguments

Dr. Vollemer's Declaration has been carefully considered and in place of working examples of antibodies meeting all of the claim limitations, they instead advance generalities. First, Dr. Vollmers does not provide any evidence by way of reduction to practice for the genus much less a reasonable number of antigens that are expressed on all of the claimed cell lines and to which both the purified antibody and the SAM-6 antibody would bind. Second, Dr. Vollmers does not establish the specificity or the exclusivity of any such purified antibody capable of recognizing the same epitope as the SAM-6 antibody and cannot do so because the exact identity of antigen(s) is unknown. Applicants would seemingly understand that in order for the ordinary artisan to perform the routine screening assays for any of the instant claimed purified antibodies, that the ordinary artisan would seemingly need to have in hand, the antigen of interest.

Here Applicants would have the Office believe that they entitled to antibodies recognizing any epitope on any antigen so long as the SAM-6 antibody binds the same epitope on the same antigen without having so much as characterized the antigen(s). They extend this illogical and sophistic allegation even further, by stating that they are entitled to variants of any one of these antibodies, when still they have not revealed the identity of the antigen to which any one of the variants can even bind."

Applicants allegations on pp. 11-15 of the response of 7/12/10 have been considered and are not found persuasive. Applicants allege in view of the guidance in

the specification and knowledge in the art at the time of the invention, the publications of record, and the previously submitted Declaration under 37C.F.R. §1.132 executed by Dr. Peter Vollmers, the skilled artisan could readily produce and identify antibody variants and functional fragments of SEQ ID NO: 1 and 3 without undue experimentation.

Response to Arguments

a) The question remains what is the antigen for the SAM6 antibody? In order for the skilled artisan to practice screening any antibody variant of SAM6 against the same antigen, and in order to establish unequivocally, that antibody binding is specific/ exclusive and not cross-reactive, how is any such screening method enabled in the absence of the antigen's identity? Applicants would have the Office believe they are entitled to a genus of antibodies against an unknown antigen and irrespective whether the genus antibodies are specific or non-specific in binding to an antigen.

b) Applicants urge the Office to believe, that despite the absence of evidence in the specification for identification of the epitope much less the antigen recognized by the SAM6 antibody, that they are entitled to ambiguous language in Claim 73 reciting "specifically binds to an epitope of an antigen expressed by at least one of….". The antibody field of art recognizes that "specific" binding encompasses exclusive and cross-reactive binding- "specific" does not exclude cross-reactive binding with another antigen much less another epitope. Accordingly, and despite Applicants urging that any antibody can be screened with cross-competing antibodies for epitope binding and is therefore universally enabled, Applicants situation is distinghuishable because the

antigen much less the epitope is not known. Also, it is not clear how varying the antibody variable domain by "at least 95%" would result in a genus of antibodies recognizing the same epitope on the same antigen, when neither have been yet been disclosed by Applicants.

c) Applicants have not shown how to screen an antibody variant of SAM6 for binding to it's cognate antigen because they have not provided the identity of the antigen. Accordingly, because the ordinary artisan cannot even determine whether binding of the SAM6 antibody of SEQ ID NOS: 1 and 3 is cross-reactive versus specific/exclusive for an antigen(s) from amongst the claimed tumor cell lines, screening antibody variants of the parent sequence is even less enabling by the specification. "[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (quoting In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993)). Also see *Rasmussen v. Smith Klein Beecham Corp.,* 413 F.3d 1318, 1325 (Fed. Cir. 2005) "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to “inventions’ consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the “inventor” would be rewarded the spoils instead of the party who demonstrated that the method actually worked.”

d) Finally, Applicants' are requested to visit the Cabic.com website or the USPTO website where they can review any of the past Biotech Customer Partnership (BCP) presentations by TC1600 on subject matter related to claiming antibodies (e.g.,

unpredictability and undue experimentation) and meeting the enablement requirement.

The rejection is maintained.

Written Description

11. The rejection of Claims 73, 80, 81, 106-112, 115, 116, 121 (and new claims 122-124) under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained.

For purposes of review, the rejection was set forth in the Office Action of 5/5/09 as follows:

"Claims 72-79, 82-88 and 98-116 are *interpreted* as being drawn to any antibody that binds the same epitope as the SAM-6 antibody, but which epitope occurs on any number of antigens expressed on the list of neoplastic cells in Claims 72-74 and which antibody may be merely cross-reactive with the SAM-6 epitope. It is the examiner's position that the only antigenic epitope disclosed in the specification as being expressed by the neoplastic cells and recognized by the SAM-6 antibody, is the O-linked carbohydrate moiety on a post-transcriptionally modified isoform of the 78-kDa GRP, designated $GRP78^{SAM-6}$.

Under the Written Description Guidelines (66 FR 1099 (Jan. 5, 2001); 1242 O.G. 168 (Jan. 30, 2001) revised training materials Mar 28, 2008), the claimed invention must meet the following criteria as set forth.

a) Actual reduction to practice: the specification did not reveal the identity of the antigen but generally characterized the antigen by immunohistochemical screening of SAM-6 against normal tissues and autologous tumor where the antigen was defined by the cancer cell-binding properties for the antibody (Example 2). SAM-6 showed no reactivity with normal tissues but different tumor tissues (Tables 3 and 4). Partial characterization of the antigen in Example 3 showed by Western blot analysis the antibody recognized proteins of 140 kDa (Figure 3A). Rauschert et al (Lab. Invest. 88:375-386 (2008); cited in the PTO 892 form of 9/19/08) later described the antigen as GRP78 and the epitope is an O-linked carbohydrate moiety.

b) Disclosure of drawings or structural chemical formulas: the specification and drawings do not show that applicant was in possession of the epitope on any antigen other than the $GRP78^{SAM-6}$ protein and to which the SAM-6 antibody binds.

c) Sufficient relevant identifying characteristics: the specification does not identify 1) a complete structure, ii) partial structure, iii) physical and/or chemical properties, or iv) functional characteristics coupled with correlation between structure and function for the epitope for the genus antigens against which any antibody could be generated and to which SAM-6 antibody binds.

d) Method of making the claimed invention: the specification teaches making and screening antibodies and selecting the SAM-6 antibody, where as evidenced by Rauschert et al (Lab. Invest. 88:375-386 (2008); cited in the PTO 892 form of 9/19/08), the antigen was identified as GRP78 and the epitope is an O-linked carbohydrate moiety.

e) Level of skill and knowledge in the art: The term "specific" binding is not an absolute, in other words, the claimed antibody is not excluded from being cross-reactive for binding the same epitope also recognized by the SAM-6 antibody. It is noted that the term "specific binding" is not used in the immunological arts to connote exclusive binding. "Specifically binds" is not art-defined as exclusive binding as evidenced by Bost et al. (Immunol. Invest. (1988) 17:577-586) and Bendayan (J. Histochem. Cytochem. (1995) 43:881-886). That an antibody "cross-reacts", i.e., binds to more than one protein sequence, does not mean that the antibody does not "specifically react" or "specifically bind" with both proteins. For example, Bost et al. describe antibodies which "cross-react" with IL-2 and HIV envelope protein, but establish that the binding of each protein is due to the presence of a homologous sequence in each protein in which 4 of 6 residues were identical (see entire document, but especially the Abstract and Discussion). Antibodies that bound either the HIV or IL-2 derived sequence, did not cross react with irrelevant peptides (e.g., "Results, page 579). Similarly, Bendayan characterizes the specific reactivity of a monoclonal antibody

produced to human proinsulin and shows that although the antibody is highly specific; it is nevertheless able to bind to not only human proinsulin, but to proinsulin from other species and even a distinct protein, glucagon, based upon conservation of an Arg-Arg dipeptide sequence in each of these molecules (see entire document). Bendayan concludes that "an antibody directed against such a sequence, although still yielding specific labeling, could reveal different molecules not related to the original antigen" (page 886, last paragraph). See also USPN 6,210,670 (Berg) "Cross-Reacting Monoclonal Antibodies Specific for E-Selectin and P-selectin". Specificity of antibody interaction with epitopes is defined by particular amino acid sequences. Consequently, it was well known in the art at the time the invention was made that antibody binding of distinct proteins was indeed specific. Applicants have not demonstrated with sufficient evidence the uniqueness or exclusiveness of any antibody recognizing and binding to the epitope on any antigen where the same epitope is recognized by the SAM-6 antibody. .

f) Predictability in the Art: Adequate written description for an antibody appears to hinge upon whether the specification provides adequate written description for the antigen. While a specification may enable making a genus of antibodies, this does not necessarily place applicant in possession of the resultant antibodies (See *In re Kenneth Alonso* October (Fed. Cir. 2008)) sustaining a lack of adequate written description rejection where "the specification teaches nothing about the structure, epitope characterization, binding affinity, specificity, or pharmacological properties common to the large family of antibodies" where the specification does not characterize the antigens to which the monoclonal antibodies must bind).

Applicants have not characterized the epitope occurring on any antigen to which the claimed antibody should specifically and exclusively bind, and therefore, the ordinary artisan could reasonably conclude that Applicants were in possession of the claimed genus of antibodies."

The rejection was maintained in the Office Action of 1/12/10 as follows:

"Applicants allegations on pp. 13-26 have been carefully considered and they are not found persuasive. The gist of the arguments is finally presented on p. 18 when Applicants address Alonso. Here they allege In contrast to the antibodies of Alonso, the claimed antibodies and functional fragments have identical specificity and bind to an epitope, namely the epitope of the antigen expressed by at least one of the specified neoplastic cells recited in the claims to which the SAM-6 antibody comprising SEQ ID NO: 1 and SEQ ID NO:3 specifically binds. Also in contrast to Alonso, the claimed antibodies and functional fragments bind to antigen expressed by at least one of 5 well defined deposited cell lines, namely BXPC-3 (ATCC Accession No. CRL-1687), 23132/87 (DSMZ Accession No. ACC 20 i), COLO-206F (DSMZ Accession No. ACC 21), COLO-699 (DSMZ Accession No. ACC 196), and LOU- NHgl (DSMZ Accession No. ACC 393) neoplastic cells.

Response to Arguments

To put it succinctly, what is the identity of the antigen(s) that places Applicants in possession of "the purified antibody" having all of the following properties:

a) binds exclusively to the same epitope on the same antigen as the SAM-6 antibody;

b) inhibits cell proliferation of 23132/87 (DSMZ Accession No. ACC 20I) cells;

c) induces apoptosis of at least one of BXPC-3 (ATCC Accession No. CRL-1687) and 23132/87 (DSMZ Accession No. ACC 201) cells; and

d) has 80%, 85%, 90% or 95% identity to the VH/VL of SAM-6 antibody?????

Applicants present "specific" binding to some alleged shared antigen amongst several cell lines and to which the "purified antibody" and the "SAM-6 antibody" binds in terms of an absolute, in other words, that the purified antibody binds only some antigen of interest albeit undefined (expressed by at least one of BXPC-3 (ATCC Accession No. CRL-1687), 23132/87 (DSMZ Accession No. ACC 201), COLO-206F (DSMZ Accession No. ACC 21), COLO-699 (DSMZ Accession No. ACC 196), or LOU-NH91 (DSMZ Accession No. ACC 393) .neoplastic cells) to which SAM-6 also binds, and not any other antigen or anywhere else on the cells lines. Applicants allege that one skilled in the art would know that the term excludes cross-reactive antibodies. It is noted that the term "specific binding" is not used in the immunological arts to connote exclusive binding. "Specifically binds" is not art-defined as exclusive binding as evidenced by Bost et al. (Immunol. Invest. (1988) 17:577-586) and Bendayan (J. Histochem. Cytochem. (1995) 43:881-886). That an antibody "cross-reacts", i.e., binds to more than one protein sequence, does not mean that the antibody does not "specifically react" or "specifically bind" with both proteins. For example, Bost et al. describe antibodies which "cross-react" with IL-2 and HIV envelope protein, but establish that the binding of each protein is due to the presence of a homologous sequence in each protein in which 4 of 6 residues were identical (see entire document, but especially the Abstract and Discussion). Antibodies that bound either the HIV or IL-2 derived sequence, did not cross react with irrelevant peptides (e.g., "Results, page 579). Similarly, Bendayan characterizes the specific reactivity of a monoclonal antibody produced to human proinsulin and shows that although the antibody is highly specific; it is nevertheless able to bind to not only human proinsulin, but to proinsulin from other species and even a distinct protein, glucagon, based upon conservation of an Arg-Arg dipeptide sequence in each of these

molecules (see entire document). Bendayan concludes that "an antibody directed against such a sequence, although still yielding specific labeling, could reveal different molecules not related to the original antigen" (page 886, last paragraph). See also USPN 6,210,670 (Berg) “Cross-Reacting Monoclonal Antibodies Specific for E-Selectin and P-selectin". Applicants' argument attempts to limit the term "specifically binds" in a manner inconsistent with the well-known and art-recognized specificity of antibody interaction with epitopes defined by particular amino acid sequences. Consequently, it was well known in the art at the time the invention was made that antibody binding of distinct proteins was indeed specific.

Furthermore, the specification does not define the term “specificity”, the binding affinities for the prophetic purified antibodies. Applicants have not demonstrated with sufficient evidence the uniqueness or exclusiveness of any claimed purified antibody recognizing and binding to the same epitope of the same antigen as the SAM-6 antibody.

Applicants allegations on pp. 15-23 have been considered and are not found persuasive. Applicants allege given the totality of: Guidance in the specification and the high level of knowledge and skill in the art with respect to antibody structure correlating with function at the time of the invention, knowledge of the light and heavy chain variable region sequences (SEQ 1D NOs: 1 and 3) and the predicted CDRs and FRs that confer binding, as also corroborated by the Exhibit B submitted herewith and the previously submitted Exhibits and Declaration under 37 C.F.R. §1.132 executed by Dr. Vollmers, the skilled artisan would know of general regions and particular residues that would be amenable to variation and would therefore be apprised of a number of sequence variants of SEQ ID NOs:l and 3 having binding activity, the claims meet the written description standard articulated by the court in Invitrogen. Further in view of the substantially greater understanding of antibody sequence structure and correlation with function in 2003 compared to 1988, and that the claimed antibodies and fragments will have the specificity of SAM-6 antibody comprising SEQ ID NOs: l and 3, and will also necessarily have sequence homology with SEQ ID NOs: l or 3, the facts of the claims under consideration are clearly distinguishable from the facts in Alonso.

Response to Arguments

For purposes of brevity and in the interest of compact prosecution, Applicants are

directed to the following source materials as guidance for the requirements in meeting written description support under 112, 1st paragraph:

a) Applicants' are requested to visit the Cabic.com website or the USPTO website where they can review any of the past Biotech Customer Partnership (BCP) presentations by TC1600 on subject matter related to claiming antibodies (e.g., structure/function correlation) and meeting written description.

b) See, for example, *Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.* (Fed. Cir. 2010) (en banc) stating in part:

> "a few broad principles hold across all cases"; "We have made clear that the written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement. *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1366-67 (Fed. Cir. 2006). Conversely, we have repeatedly stated that actual "possession" or reduction to practice outside of the specification is not enough. Rather, as stated above, it is the specification itself that must demonstrate possession. And while the description requirement does not demand any particular form of disclosure, *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008), or that the specification recite the claimed invention *in haec verba*, a description that merely renders the invention obvious does not satisfy the requirement, *Lockwood v. Am. Airlines*, 107 F.3d 1565, 1571-72 (Fed. Cir. 1997)."
>
> "For example, a generic claim may define the boundaries of a vast genus of chemical compounds, and yet the question may still remain whether the specification, including original claim language, demonstrates that the applicant has invented species sufficient to support a claim to a genus. The problem is especially acute with genus claims that use functional language to define the boundaries of a claimed genus. In such a case, the functional claim may simply claim a desired result, and may do so without describing species that achieve that result. But the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus."

c) MPEP 2144.08 states in part:

"In the area of biotechnology, an exemplified species may differ from a claimed species by a conservative substitution ("the replacement in a protein of one amino acid by another, chemically similar, amino acid... [which] is generally expected to lead to either no change or only a small change in the properties of the protein." Dictionary of Biochemistry and Molecular Biology 97 (John Wiley & Sons, 2d ed. 1989)). The effect of a conservative substitution on protein function depends on the nature of the substitution and its location in the chain. Although at some locations a conservative substitution may be benign, in some proteins only one amino acid is allowed at a given position. For example, the gain or loss of even one methyl group can destabilize the structure if close packing is required in the interior of domains. James Darnell et al., Molecular Cell Biology 51 (2d ed. 1990)."

d) See for example, *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."; "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when … the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)).

The rejection is maintained.

New Grounds for Objection

Specification/ Sequence Listing

New Matter

12. The amendment to the specification in the Response of 7/12/10 to change the sequence for the VH CDR3 domain from residues "Lys-Thr" to "Arg-Pro" constitutes new matter. The Sequence Listing of 5/15/06 recites the original residues for SAM 6 VH ("Lys-Thr") and does not support the amendment.

Applicants revised Sequence Listing of 7/12/10 does not rectify the absence of original written description support for the amendments to SEQ ID NOS: 3 and 4. Applicants have not provided any explanation why residues 106 and 107 have been corrected to amend the VH CDR3 domain from residues "Lys-Thr" to "Arg-Pro" on p. 10 of the Response of 7/12/10.

Applicants allege on p. 9 of the Response of 7/12/10, that support for the VH sequence is shown on p. 61, lines 23-26 of the specification. However, the Examiner's search of this page amongst all of the other pages does not identify support for this amendment. The only support in the specification for "Arg-Pro" is in the SAM6 VL CDR2 domain.

This is a new matter objection for both the specification and revised Sequence Listing.

Specification

13. The amendment to the specification to enter the name and address of depository in addition to the date of hybridoma deposit is entered. However, upon closer inspection of the deposit receipt provided in the Response of 7/12/10, the Examiner notes that the date of deposit is actually *April 3, 2008*, and not April 14, 2008.

Correction is required.

Claim Objections

14. Claims 109 and 110 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 109 and 110 recite identical limitations that have been introduced into Claim 73 in the Response of 7/12/10.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description/ New Matter

15. Claims 111 and 124 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 111 and 124 are interpreted as being drawn to the VH CDR3 of DEQ ID NO:3 having the following sequence: "Asp-Arg-Leu-Ala-Val-Ala-Gly-Arg-Pro-Phe-Asp-Tyr (CDR3) SEQ ID NO:3."

The examiner's search of the specification for the limitation does not identify literal support for this limitation. (MPEP 706.03(m) states in part "New matter includes not only the addition of wholly unsupported subject matter, but may also include adding specific percentages or compounds after a broader original disclosure, or even the omission of a step from a method. See MPEP § 608.04 to § 608.04(c). See In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976) and MPEP § 2163.05 for guidance in determining whether the addition of specific percentages or compounds after a broader original disclosure constitutes new matter.")

This is a new matter rejection.

Enablement

16. Claims 73, 80, 81, 106-112, 115, 116 and 122-124 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

Nature of the Invention

In the case where the antigen has not even been identified by Applicants original disclosure, Applicants have now made matters even more complicated by amending the claims to encompass a single domain antibody having the VL CDRs or the VH CRDs from SEQ ID NO: 1 or 3, respectively. The claims are examined for enablement with respect to the ability of a single domain antibody to an unknown antigen.

Disclosure in the Specification

There is no original disclosure for a single domain antibody comprising the VL or VH CDRs from the SAM6 antibody. Applicants have proffered new evidence in the way of an additional experiment showing that the SAM6 VH domain can bind to HeLa cells in Exhibit B.

Applicants have not identified the source of these data, the person(s) averring attesting to these data, and the relationship of these data to any pending claims.

Accordingly, the evidence has not been considered. Applicants are advised to enter the extrinsic evidence under a 1.132 Declaration meeting the requirements of37 CFR 1.132 and MPEP 2164.05.

Prior Art Status: Single Variable Domain Antibodies are unpredictable in binding

The single domain antibodies taught in WO 2004/003019 (Domantis) and Ward et al. (Nature 341:544-546 (1989)) appear to be limited examples of single domain antibodies generated against a limited number of antigens that have been shown to retain antigen binding specificity. However, Ward teaches and cautions:

"Separated heavy and light chains have previously been identified with antigen or hapten binding activities although the affinities were poor, with no evidence for binding by single chains rather than dimers" (p. 544, Col. 2) and

"However, VH domains are relatively sticky, presumably due to the exposed hydrophobic surface normally capped by the VH and VL domains" (p. 546, Col. 1).

By and large, the art recognizes that single domain antibodies do not provide the sufficient contact sites for antigen binding or at the very least the molecules tend to be less soluble and otherwise form aggregates.

Smith-Gill et al. (J. Immunol. 139:4135-4144 (1987); cited in the PTO 892 form of 9/19/08) observed from chain recombination experiments that through interactions between the VH/VL pair, specificity for antigen is H chain determined, specific binding is increased when L chains of the same parental isotype are used, and that both H and L chains determine fine specificity.

Kumar et al. (J. Biol. Chem. 275:35129-35136 (2000); cited in the PTO 892 form of 9/19/08) discloses Fab molecules with anti-DNA (light chain) and anti-cardiolipin (heavy chain) binding activities, and that pairing of the partner chains is dependent on the particular H/L chain pairing.

Song et al. (Biochem Biophys Res Comm 268:390-394 (2000); cited in the PTO 892 form of 9/19/08) discloses that affinity and specificity of scFv for preS1 protein of HBV is dependent on S-S bond formation in conferring correct refolding of the fragments for retaining binding properties, and that L chains are predominant in antigen binding.

Therefore, selecting and producing just any variable domain substituted antibody with the ability to properly associate and assemble into a fully functional antibody which maintains the binding specificity for an antigen would be highly unpredictable based on the methods described in the specification and the prior art disclosures.

Unpredictability/ Undue Experimentation

Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Furthermore, while the level of skill required to generate the antibodies is that of a molecular immunologist, the artisan of ordinary skill in the art would have been required to produce and express the modified antibodies, measure binding characteristics (e.g., binding specificity, equilibrium dissociation constant (K_D), dissociation and association rates (K_{off} and K_{on} respectively), and binding affinity and/or avidity compared with the parent antibody), and then finally perform bioassays to identify any one or more of the

characteristics of an antibody. The technology to perform these experiments was available at the time of application filing, but the amount of experimentation required to generate even a single antibody meeting all of the claim limitations would not have been routine much less could one of ordinary skill in the art predict that any one clone VH or VL clone encompassed by the claims would have retained the antigen binding activity (MPEP 2164.06, "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (In re Wands, 858 F.2d 731, 737, 8 USQP2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

MPEP 2138.05 *Birmingham v. Randall*, 171 F.2d 957, 80 USPQ 371, 372 (CCPA 1948) "To establish an actual reduction to practice of an invention directed to a method of making a product, it is not enough to show that the method was performed. "[S]uch an invention is not reduced to practice until it is established that the product made by the process is satisfactory, and [ ] this may require successful testing of the product."

Conclusion

17. No claims are allowed.

18. The VL (SEQ ID NO:1) and VH (SEQ ID NO:3) domains of the SAM-6 antibody are free from prior art.

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn Bristol/
Primary Examiner, Art Unit 1643